I RESEARCH

**I Research: Journal of Pharmacology**
www.iresearchonline.com

# Neuroprotective Effect of Apigenin and Omega-3 Fatty Acids on Cholinergic Dysfunction and Oxidative Stress in Scopolamine Induced Cognitive Impairment in Rats

Thiruselvam V* and Marihrishnaa K.

*Department of Pharmacology, K.M College of Pharmacy, The Tamil Nadu Dr. M.G.R Medical University, Chennai, Tamil Nadu, India*

**ARTICLE INFO**

***Keywords:***
*Apigenin,*
*Omega-3 fatty acid,*
*Scopolamine,*
*Alzheimer's disease,*
*Oxidative stress,*
*Acetylcholinesterase,*
*Neuroprotection*

***Article History:***
*Received : 25th September 2026*
*Accepted : 28th September 2026*
*Available online : 28th September 2026*

**ABSTRACT**

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cholinergic dysfunction, oxidative stress, and hippocampal neuronal loss. Scopolamine, a muscarinic receptor antagonist, is widely used to induce reversible cognitive impairment in rodents that reproduces key biochemical and behavioural hallmarks of AD. Apigenin, a naturally occurring flavonoid, and omega-3 fatty acids have each been reported to possess antioxidant and neuroprotective properties, but their combined effect against scopolamine-induced neurotoxicity has not been well characterised.

Objective: To evaluate the neuroprotective effect of apigenin, alone and in combination with omega-3 fatty acid, on cholinergic function and oxidative stress in a scopolamine-induced model of cognitive impairment in rats.

Methods: Adult Wistar albino rats were divided into six groups (n = 3/group): normal control, scopolamine (1 mg/kg, i.p., days 9–17) toxic control, donepezil (10 mg/kg, p.o.) standard control, apigenin low dose (25 mg/kg), apigenin high dose (50 mg/kg), and a combined apigenin (25 mg/kg) plus omega-3 fatty acid (100 mg/kg) group, all treated orally for 17 days alongside scopolamine. Spatial learning and memory were assessed by the Morris water maze (escape latency), and locomotor activity by digital actophotometer, on days 0, 9, 14, and 17. On day 17, brain acetylcholinesterase (AChE) activity and the oxidative stress markers malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) were estimated, and hippocampal sections were examined histopathologically (H&E staining).

Results: Scopolamine produced significant cognitive and locomotor impairment, elevated AChE activity and MDA levels, depleted GSH, SOD, and CAT, and caused marked hippocampal degeneration compared with the normal control group ($p < 0.001$). Apigenin treatment attenuated these changes in a dose-dependent manner, and the combined apigenin–omega-3 fatty acid group showed the greatest improvement across behavioural, biochemical, and histopathological parameters, approaching values recorded in the standard (donepezil) group.

Conclusion: Apigenin exerts a dose-dependent neuroprotective effect against scopolamine-induced cognitive dysfunction, and its combination with omega-3 fatty acid produces a more pronounced protective response, indicating a complementary antioxidant and cholinergic-restorative action that supports further investigation of this combination as a candidate neuroprotective strategy.

## Introduction

Neurotoxicity refers to adverse structural or functional changes in the central or peripheral nervous system caused by biological, chemical, or physical agents, ranging from transient functional disturbance to permanent neuronal injury[1]. Neurons, the fundamental signalling units of the nervous system, depend on intact cholinergic transmission, redox homeostasis, and structural integrity of synaptic membranes for normal cognitive function. Disruption of any of these processes, whether by environmental neurotoxins, metabolic disturbance, or neurodegenerative disease, can manifest as impaired learning, memory loss, and behavioural change [2].

Alzheimer's disease (AD) is the most common cause of dementia worldwide and is characterised by progressive cognitive decline, cholinergic deficits, chronic oxidative stress, and accumulation of amyloid-beta and hyperphosphorylated tau in the hippocampus and

* Corresponding author
✉: Thiruselvam V: thiruspharma@gmail.com

cerebral cortex [3]. Among the mechanisms implicated in AD pathogenesis, loss of cholinergic neurotransmission and oxidative damage to neuronal membranes are considered central contributors to the cognitive deficits observed clinically and experimentally.

Scopolamine, a non-selective muscarinic acetylcholine receptor antagonist, is one of the most extensively used pharmacological tools for modelling cognitive impairment in rodents. By blocking central muscarinic receptors, scopolamine reproduces the cholinergic deficit and associated oxidative stress seen in AD, making the scopolamine-induced amnesia model a well-validated and reproducible platform for evaluating candidate neuroprotective and pro-cognitive agents [4].

Apigenin (4′,5,7-trihydroxyflavone) is a naturally occurring flavonoid found abundantly in parsley, celery, chamomile, and citrus fruits. It is known to cross the blood–brain barrier and has been reported to exhibit antioxidant, anti-inflammatory, and neuroprotective actions, including modulation of brain-derived neurotrophic factor (BDNF) and CREB signalling pathways relevant to synaptic plasticity and memory. Omega-3 polyunsaturated fatty acids, principally EPA and DHA, are essential structural components of neuronal membranes and have been independently associated with improved cognitive outcomes, reduced neuroinflammation, and protection against age-related and toxin-induced cognitive decline. Given their distinct but potentially complementary mechanisms, the combined administration of apigenin and omega-3 fatty acid may offer additive or synergistic neuroprotection that has not been directly evaluated in the scopolamine model.

The present study was therefore designed to evaluate the neuroprotective potential of apigenin, alone at two dose levels and in combination with omega-3 fatty acid, against scopolamine-induced cholinergic dysfunction, oxidative stress, and hippocampal neuronal damage in Wistar albino rats, using an integrated panel of behavioural, biochemical, and histopathological endpoints.

## Materials and Methods

The study aimed to evaluate the neuroprotective effect of apigenin and omega-3 fatty acid on cholinergic dysfunction and oxidative stress in scopolamine-induced cognitive impairment in rats, with specific objectives of assessing behavioural performance, brain AChE activity, antioxidant enzyme status, and hippocampal histopathology following treatment.

### *Animals*

Adult Wistar albino rats (both sexes, aged 20–24 weeks, body weight 190–220 g) were procured and housed in the animal facility of K.M. College of Pharmacy, Madurai. Animals had free access to a standard pelleted diet and water, were maintained under controlled conditions (temperature 23 ± 1 °C, relative humidity 50 ± 10%, 12 h light/dark cycle), and were acclimatised for 15 days prior to the start of the experiment. All procedures were conducted in accordance with CPCSEA guidelines and approved by the Institutional Animal Ethics Committee, K.M. College of Pharmacy, Madurai (Proposal No. IAEC/THIRUSELVAMV/TNMGRMU/M.PHARM/KMCP/07/2025-2026).

### *Drugs and chemicals*

Apigenin was procured from BLD Pharmatech Pvt. Ltd., Hyderabad, India. Scopolamine, omega-3 fatty acid, and donepezil were procured from SM Pharma & Chemicals, Mumbai, India. All other reagents used were of analytical grade.

### *Experimental design*

Eighteen rats were randomly allocated into six groups of three animals each, as summarised in Table 1.

**Table 1. Experimental groups and treatment protocol**

| Group | Treatment | Dose | Route | Schedule |
|---|---|---|---|---|
| **I** | Normal control | Normal saline | Oral | Days 1–17 |
| **II** | Toxic control | Scopolamine 1 mg/kg | i.p. | Days 9–17 |
| **III** | Standard control | Donepezil 10 mg/kg + Scopolamine 1 mg/kg | Oral + i.p. | Donepezil days 1–17; Scopolamine days 9–17 |
| **IV** | Apigenin low dose | Apigenin 25 mg/kg + Scopolamine 1 mg/kg | Oral + i.p. | Apigenin days 1–17; Scopolamine days 9–17 |
| **V** | Apigenin high dose | Apigenin 50 mg/kg + Scopolamine 1 mg/kg | Oral + i.p. | Apigenin days 1–17; Scopolamine days 9–17 |
| **VI** | Combined treatment | Apigenin 25 mg/kg + Omega-3 FA 100 mg/kg + Scopolamine 1 mg/kg | Oral + i.p. | Apigenin + Omega-3 days 1–17; Scopolamine days 9–17 |

Apigenin was suspended in 0.5% carboxymethyl cellulose; omega-3 fatty acid was suspended in olive oil; scopolamine and donepezil were prepared in normal saline. Scopolamine (1 mg/kg, i.p.) was administered once daily from day 9 to day 17 to induce cholinergic dysfunction and oxidative stress.

### *Behavioural Assessment*

***Morris Water Maze (MWM) Test:*** Spatial learning and hippocampus-dependent memory were assessed using a circular water maze (90 cm diameter, 37 cm height) filled

with opacified water maintained at 24 ± 2 °C, containing a submerged escape platform positioned in a fixed target quadrant. Each animal underwent an initial habituation swim, followed by acquisition trials in which the time taken to locate the hidden platform (escape latency) was recorded on days 0, 9, 14, and 17[5].

***Locomotor Activity:*** Spontaneous locomotor (gross behavioural) activity was recorded using a digital actophotometer for 10 minutes per animal at the same time points, based on interruption counts of a photoelectric beam[8].

### *Biochemical Estimations*

On day 17, animals were euthanised 24 h after the final behavioural assessment; brains were rapidly excised, rinsed in ice-cold saline, and homogenised (10% w/v) in 0.1 M phosphate buffer (pH 7.4). The homogenate was centrifuged (1000 × g, 20 min, 4 °C) and the supernatant used for the following assays:

- Acetylcholinesterase (AChE) activity — Ellman's colorimetric method, measuring the rate of thiocholine-DTNB product formation at 412 nm
- Malondialdehyde (MDA), an index of lipid peroxidation — thiobarbituric acid reactive substances (TBARS) assay, read at 532 nm
- Reduced glutathione (GSH) — DTNB-based colorimetric assay, read at 412 nm
- Superoxide dismutase (SOD) — inhibition of nitroblue tetrazolium reduction, read at 560 nm
- Catalase (CAT) — decomposition of $H_2O_2$ monitored at 240 nm

### *Histopathological Examination*

Brain tissue was fixed in 10% neutral buffered formalin, dehydrated, embedded in paraffin, sectioned, stained with haematoxylin and eosin (H&E), and examined by light microscopy for hippocampal neuronal integrity, vacuolation, pyknosis, and plaque-like deposition.

### *Statistical Analysis*

Data are expressed as mean ± SEM. Inter-group differences were analysed by one-way ANOVA followed by the Student–Newman–Keuls post hoc test (GraphPad InStat v3.0). Behavioural data recorded across multiple days were analysed by two-way repeated-measures ANOVA followed by Bonferroni's post hoc test. A value of $p < 0.05$ was considered statistically significant.

## Results

### *Effect on spatial learning and memory (Morris water maze)*

Scopolamine-treated animals (Group II) showed a significant increase in escape latency relative to normal controls ($p < 0.001$), indicating impaired spatial learning and memory. Treatment with donepezil, apigenin (both doses), and the apigenin–omega-3 combination progressively reduced escape latency across days 9, 14, and 17 ($p < 0.05$–$0.001$ vs. Group II). The apigenin high-dose group performed significantly better than the low-dose group, and the combined apigenin–omega-3 group showed the greatest improvement among the apigenin-treated groups, approaching values recorded for the standard drug group (Table 2, Fig. 1).

**Table 2. Effect on escape latency (seconds) in the Morris water maze test**

| Group | Day 0 | Day 9 | Day 14 | Day 17 |
|---|---|---|---|---|
| **I — Normal control** | 47.0 ± 0.85 | 33.70 ± 0.80 | 25.8 ± 0.65 | 20.5 ± 0.61 |
| **II — Toxic control** | 57.5 ± 1.52 | 56.0 ± 0.68**a | 54.5 ± 0.84**a | 52.7 ± 1.08**a |
| **III — Standard** | 56.2 ± 0.66 | 35.30 ± 0.74*b | 28.78 ± 0.68**b | 21.17 ± 0.60**b |
| **IV — Apigenin low dose** | 53.2 ± 0.65 | 44.20 ± 0.70*b | 33.5 ± 0.67**b | 31.8 ± 0.70**b |
| **V — Apigenin high dose** | 58.5 ± 0.61 | 46.17 ± 0.47*b | 43.5 ± 0.42**b | 30.17 ± 0.74**b |
| **VI — Apigenin + Omega-3** | 55.7 ± 0.84 | 46.70 ± 0.55*b | 31.3 ± 0.71**b | 23.85 ± 0.61**b |

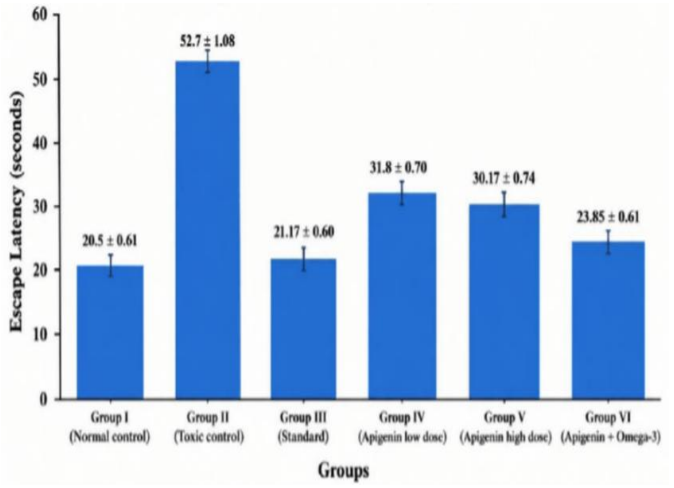


*Fig. 1. Escape latency (seconds) in the Morris water maze test on day 17 across treatment groups.*

### *Effect on Locomotor Activity*

Scopolamine administration significantly reduced spontaneous locomotor activity compared with normal controls ($p < 0.001$), confirming suppression of exploratory behaviour. All treated groups showed a significant, time-dependent recovery in locomotor counts relative to Group II ($p < 0.001$), with the combined apigenin–omega-3 group showing the most complete restoration among the apigenin-based regimens (Table 3, Fig. 2).

**Table 3. Effect on locomotor activity (actophotometer counts)**

| Group | Day 0 | Day 9 | Day 14 | Day 17 |
|---|---|---|---|---|
| **I — Normal control** | 238 ± 13.7 | 242 ± 15.2 | 268 ± 16.5 | 280 ± 17.8 |
| **II — Toxic control** | 232 ± 12.9 | 158 ± 13.8**a | 142 ± 14.6**a | 135 ± 14.2**a |
| **III — Standard** | 240 ± 14.2 | 190 ± 14.7**b | 225 ± 15.8**b | 250 ± 16.5**b |
| **IV — Apigenin low dose** | 235 ± 13.8 | 170 ± 14.1**b | 185 ± 15.2**b | 195 ± 15.8**b |
| **V — Apigenin high dose** | 237 ± 14.1 | 185 ± 14.5**b | 210 ± 15.5**b | 225 ± 16.2**b |
| **VI — Apigenin + Omega-3** | 239 ± 13.9 | 205 ± 15.1**b | 242 ± 16.1**b | 265 ± 17.1**b |

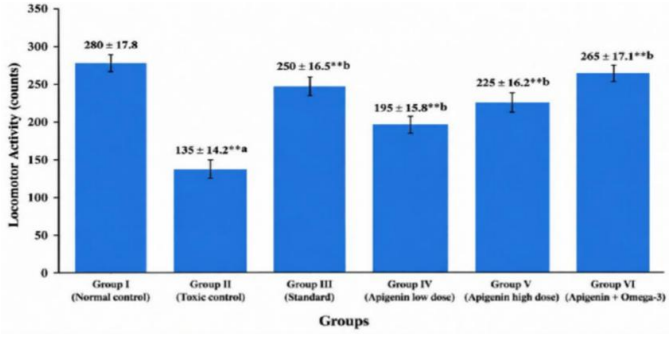


*Fig. 2. Locomotor activity (counts) on day 17 across treatment groups.*

### *Effect on Brain Acetylcholinesterase (AChE) Activity*

Chronic scopolamine administration significantly increased brain AChE activity relative to normal controls ($p < 0.01$), consistent with cholinergic dysfunction. Donepezil, apigenin at both doses, and the apigenin–omega-3 combination significantly attenuated this rise ($p < 0.01$ vs. Group II), with the combined treatment group showing AChE activity closest to the standard drug group (Table 4, Fig. 3).

**Table 4. Effect on brain acetylcholinesterase (AChE) activity**

| Group | Treatment | AChE (nmol ATCI hydrolysed/min/mg protein) |
|---|---|---|
| **G1** | Normal control | 2.4 ± 0.34 |
| **G2** | Toxic control | 8.9 ± 0.96*a |
| **G3** | Standard control | 3.8 ± 0.49*b |
| **G4** | Apigenin low dose | 4.9 ± 0.58*b |
| **G5** | Apigenin high dose | 4.5 ± 0.66*b |
| **G6** | Combined treatment | 4.1 ± 0.54*b |

*Values are mean ± SEM (n = 3), analysed by one-way ANOVA followed by Newman–Keuls test. *a $p < 0.01$ vs. normal control; *b $p < 0.01$ vs. toxic control.*

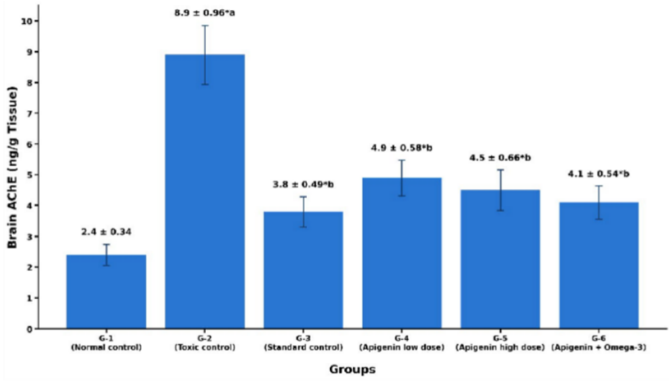


*Fig. 3. Brain acetylcholinesterase (AChE) activity across treatment groups.*

### Effect on Oxidative Stress and Antioxidant Parameters

Scopolamine significantly increased MDA (lipid peroxidation) and decreased GSH, SOD, and CAT levels compared with normal controls ($p < 0.01$), reflecting a state of oxidative stress and impaired antioxidant defence. Treatment with apigenin at both doses significantly reversed these alterations, and the combined apigenin–omega-3 group consistently showed the most pronounced normalisation among the apigenin-treated groups across all four parameters (Table 5, Figs. 4–7).

**Table 5. Effect on oxidative stress and antioxidant enzyme parameters**

| Group | MDA (nmol/mg protein) | GSH (µmol/mg protein) | SOD (U/mg protein) | CAT (U/mg protein) |
|---|---|---|---|---|
| **G1 — Normal control** | 19.4 ± 1.08 | 1.56 ± 0.58 | 284.10 ± 6.35 | 0.85 ± 0.18 |
| **G2 — Toxic control** | 52.2 ± 3.74*a | 0.46 ± 0.18*a | 135.2 ± 4.64*a | 0.35 ± 0.08*a |
| **G3 — Standard** | 24.7 ± 1.40*b | 1.36 ± 0.39*b | 253.4 ± 5.77*b | 0.77 ± 0.16*b |
| **G4 — Apigenin low** | 30.9 ± 2.05*b | 0.95 ± 0.31*b | 212.3 ± 5.26*b | 0.54 ± 0.12*b |
| **G5 — Apigenin high** | 28.15 ± 2.30*b | 1.14 ± 0.22*b | 238.7 ± 4.64*b | 0.66 ± 0.10*b |
| **G6 — Combined** | 26.42 ± 1.69*b | 1.27 ± 0.33*b | 244.9 ± 5.46*b | 0.71 ± 0.14*b |

*Values are mean ± SEM (n = 3). *a $p < 0.01$ vs. normal control; *b $p < 0.01$ vs. toxic control.*

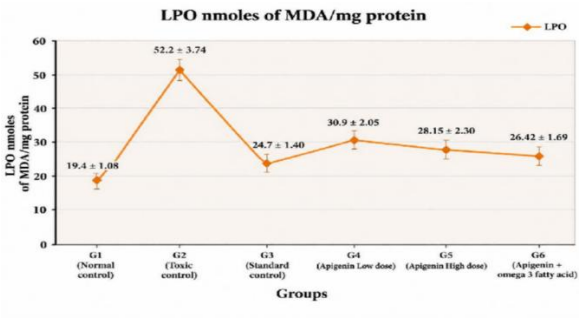


*Fig. 4. Malondialdehyde (MDA / lipid peroxidation) levels across treatment groups.*

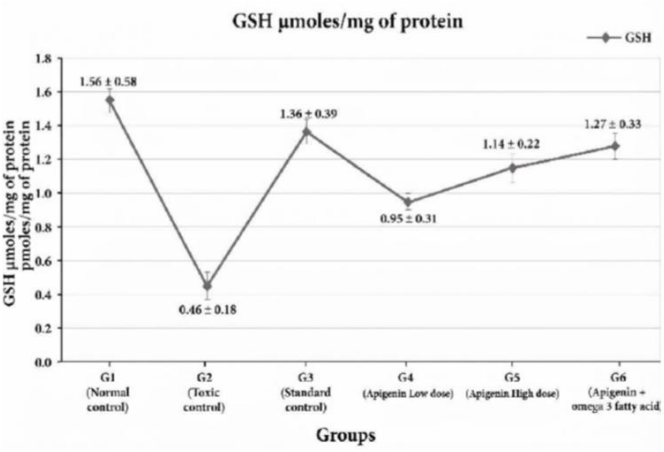


*Fig. 5. Reduced glutathione (GSH) levels across treatment groups.*

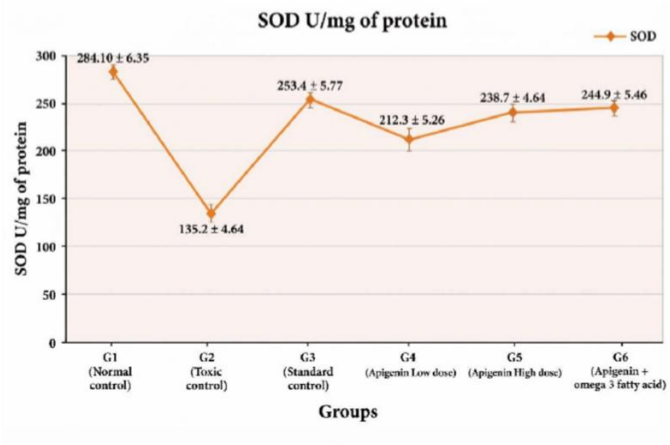


*Fig. 6. Superoxide dismutase (SOD) activity across treatment groups.*

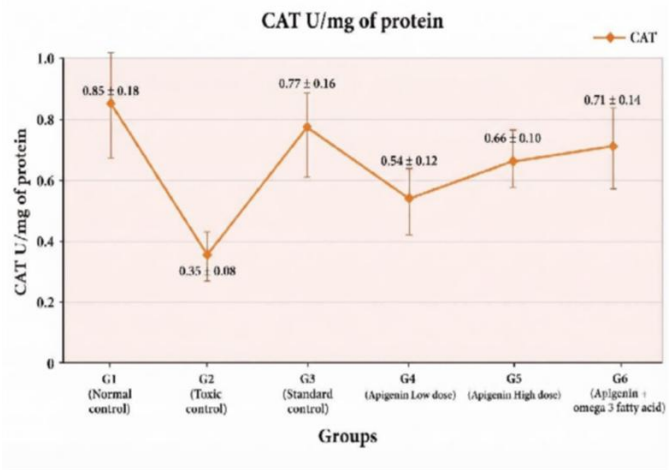


*Fig. 7. Catalase (CAT) activity across treatment groups.*

### *Histopathological Findings*

Photomicrographs of H&E-stained hippocampal sections are shown in Fig. 8. Normal control tissue (Group I) displayed well-organised, uniformly distributed neuronal architecture with no vacuolation, pyknosis, or plaque-like deposition. Toxic control tissue (Group II) showed extensive vacuolar degeneration, numerous pyknotic nuclei, and dense plaque-like deposits, consistent with marked scopolamine-induced hippocampal neurotoxicity. Standard-drug (Group III) and apigenin-treated sections (Groups IV and V) showed progressively better preservation of hippocampal architecture in a dose-dependent manner. The combined apigenin–omega-3 group (Group VI) exhibited the most complete protection, with near-normal hippocampal architecture, minimal vacuolation, and markedly reduced plaque-like deposits, closely resembling both the standard drug and normal control groups.

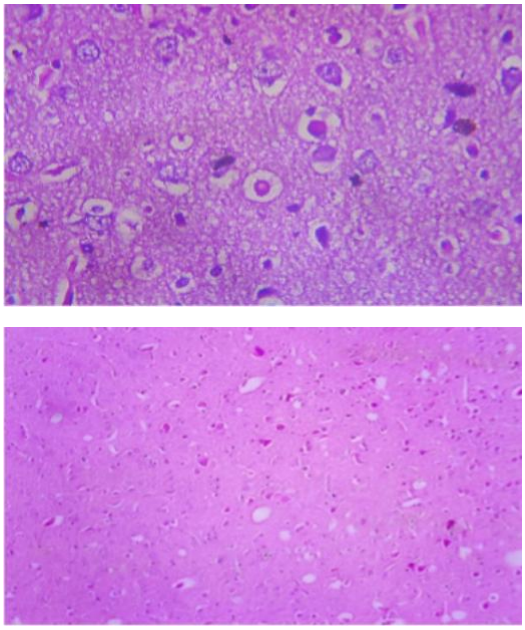

*Fig. 8a–b. Hippocampal histopathology — (a) Group I, normal control, showing intact architecture; (b) Group II, toxic control, showing extensive vacuolar degeneration and plaque-like deposits.*

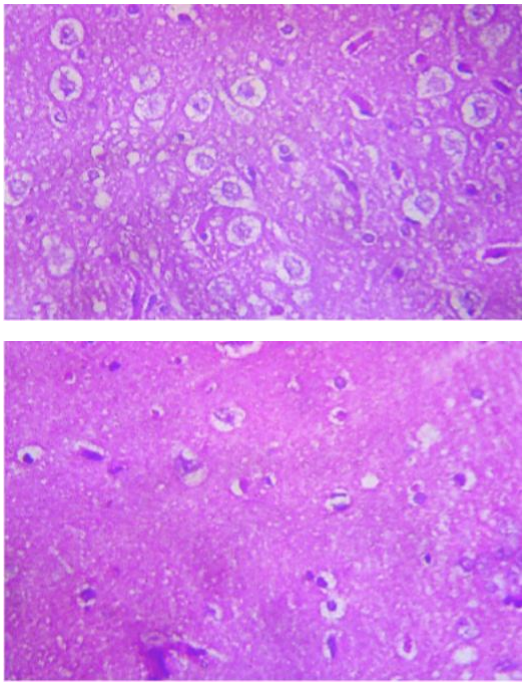

*Fig. 8c–d. (c) Group III, standard drug, showing relatively preserved architecture; (d) Group IV, apigenin low dose, showing partial protection with moderate vacuolation.*

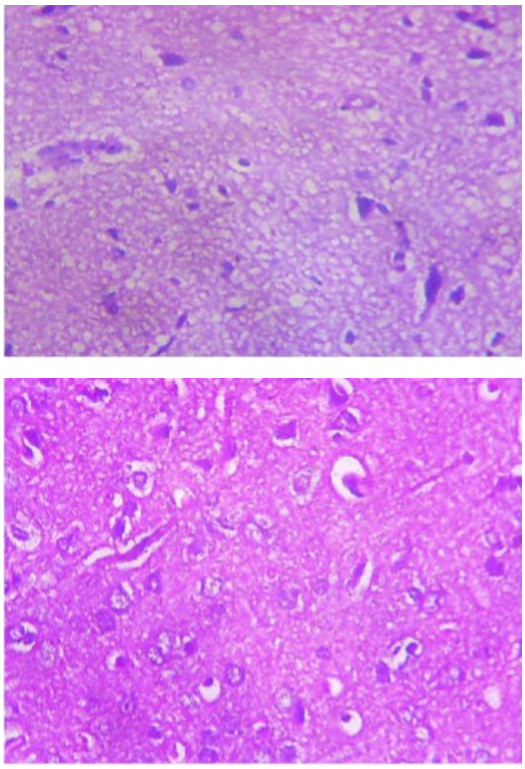

*Fig. 8e–f. (e) Group V, apigenin high dose, showing dose-dependent improvement; (f) Group VI, apigenin + omega-3 fatty acid, showing near-normal architecture with minimal vacuolation.*

## Discussion

The scopolamine-induced amnesia model reproduces central cholinergic hypofunction and secondary oxidative stress, two mechanisms strongly implicated in Alzheimer's disease pathology[18]. In the present study, chronic scopolamine exposure produced the expected constellation of deficits: prolonged escape latency in the Morris water maze, suppressed locomotor activity, elevated brain AChE activity, increased lipid peroxidation, depletion of GSH, and reduced SOD and CAT activity, accompanied by marked hippocampal degeneration on histopathology. These findings collectively confirm successful induction of a cholinergic-and oxidative-stress-mediated cognitive deficit consistent with previous reports using this model[3].

Treatment with apigenin improved performance across all endpoints in a dose-dependent manner, with the high-dose group consistently outperforming the low-dose group. This is consistent with earlier reports that apigenin improves spatial memory and attenuates neuronal damage in scopolamine-treated animals[13], an effect attributed in part to its capacity to scavenge reactive oxygen species and support endogenous antioxidant defence, alongside modulation of neurotrophic signalling pathways relevant to synaptic function.

The most notable finding of the present study was the consistently superior performance of the combined apigenin–omega-3 fatty acid group relative to apigenin monotherapy at either dose, across behavioural, biochemical, and histological measures. This pattern suggests a complementary, rather than purely additive, interaction between the two agents: apigenin's established antioxidant and anti-inflammatory actions may act alongside the structural and functional membrane-stabilising properties of omega-3 fatty acids, which are known to support neuronal membrane integrity and modulate cellular oxidative balance[28]. The near-restoration of AChE activity and antioxidant enzyme levels toward normal-control values in the combined group, together with the closest-to-normal hippocampal histology among the apigenin-based regimens, supports this interpretation.

The reduction in AChE activity observed with apigenin treatment is of particular mechanistic interest, since restoration of cholinergic tone is the pharmacological basis for the standard-of-care cholinesterase inhibitors used clinically in AD. While donepezil produced the most direct cholinergic effect as expected of a selective AChE inhibitor, the apigenin–omega-3 combination achieved comparable biochemical and histological protection through what is likely a predominantly antioxidant- and membrane-protective mechanism, indicating that multiple, non-mutually-exclusive pathways can converge on a similar neuroprotective outcome.

Taken together, these findings support the hypothesis that oxidative stress and cholinergic dysfunction are mechanistically linked contributors to scopolamine-induced cognitive impairment, and that combination therapy targeting both pathways, through a natural flavonoid and an essential fatty acid, may offer a favourable neuroprotective profile relative to either agent alone. Given the good tolerability generally reported for both apigenin and omega-3 fatty acids, this combination may merit further investigation as an adjunct or complementary strategy in models of cholinergic and oxidative-stress-related cognitive decline.

## Conclusion

Chronic scopolamine administration produced significant cognitive impairment, cholinergic dysfunction, and oxidative damage in rats, along with hippocampal neuronal degeneration. Apigenin, at both low and high doses, exerted a significant, dose-dependent neuroprotective effect against these alterations. Combining apigenin with omega-3 fatty acid produced a more consistent and pronounced improvement across behavioural, biochemical, and histopathological parameters than apigenin alone, indicating a favourable combined antioxidant, cholinergic-restorative, and neuroprotective action. These findings support further preclinical evaluation of the apigenin–omega-3 fatty acid

combination as a candidate strategy for attenuating scopolamine-induced, and potentially broader oxidative-stress-related, cognitive dysfunction.

## Acknowledgement

The authors thank the Department of Pharmacology, K.M. College of Pharmacy, Madurai, for providing the facilities used in this study.

## References

1. Cunha-Oliveira T, Rego AC, Oliveira CR. Cellular and molecular mechanisms involved in the neurotoxicity of opioid and psychostimulant drugs. Brain Res Rev. 2008;58(1):192-208.
2. Watkins KD, Wexler P. History of toxicology. In: Wexler P, editor. Information Resources in Toxicology. 4th ed. Amsterdam: Elsevier; 2009. p. 11-29.
3. Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. Nat Rev Dis Primers. 2021;7(1):33.
4. Haider S, Tabassum S, Perveen T. Scopolamine-induced greater alterations in neurochemical profile and increased oxidative stress demonstrated a better model of dementia: a comparative study. Brain Res Bull. 2016;127:234-47.
5. Vorhees CV, Williams MT. Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc. 2006;1(2):848-58.
6. Morris RGM. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods. 1984;11(1):47-60.
7. Brandeis R, Brandys Y, Yehuda S. The use of the Morris water maze & gross behavioural in the study of memory and learning. Int J Neurosci. 1989;48:29-69.
8. Dunham NW, Miya TS. A note on a simple apparatus for detecting neurological deficit in rats and mice. J Am Pharm Assoc. 1957;46(3):208-9.
9. Ellman GL, Courtney KD, Andres V Jr, Featherstone RM. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem Pharmacol. 1961;7:88-95.
10. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem. 1979;95(2):351-8.
11. Ellman GL. Tissue sulfhydryl groups. Arch Biochem Biophys. 1959;82(1):70-7.
12. Bhattacharjee B, Shakya A, Shivavedi N, Sahu RK, Sandhanam K. Exploring the combined neuroprotective effects of resveratrol and hesperidin in a scopolamine-induced rat model of cognitive impairment. Neuroscience. 2025;579:54.
13. Kim YJ, Kim JH, He MT, Lee AY, Cho EJ. Apigenin ameliorates scopolamine-induced cognitive dysfunction and neuronal damage in mice. Molecules. 2021;26(17):5192.
14. Vogel HG. Drug Discovery and Evaluation: Pharmacological Assays. 3rd ed. Berlin: Springer; 2008.
15. Halliwell B, Gutteridge JMC. Free Radicals in Biology and Medicine. 5th ed. Oxford: Oxford University Press; 2015.
16. Ajami M, Eghtesadi S, Habibey R, Mirzay Razaz J, Peyrovi H, Zarrindast M, et al. Effect of short and long-term treatment with omega-3 fatty acids on scopolamine-induced amnesia. Iran J Pharm Res. 2012;11(2):533-40.
17. Foudah AI, Devi S, Alam A, Salkini MA, Ross SA. Anticholinergic effect of resveratrol with vitamin E on scopolamine-induced Alzheimer's disease in rats: mechanistic approach to prevent inflammation. Front Pharmacol. 2023;14:1115721.
18. Klinkenberg I, Blokland A. The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies. Neurosci Biobehav Rev. 2010;34(8):1307-50.
19. Assi AA, Abdelnabi S, Attaai A, Abd-ellatief RB. Effect of ivabradine on cognitive functions of rats with scopolamine-induced dementia. Sci Rep. 2022;12:16970.
20. Zhang N, Nao J, Dong X. Efficacy and safety of natural apigenin treatment for Alzheimer's disease: focus on in vivo research advancements. Curr Neuropharmacol. 2025;23(6):728-54.
21. Oyagbemi AA, Femi-Akinlosotu OM, Obasa AA, Ojo MS, Salami AT, Ajibade TO, et al. Apigenin mitigates oxidative stress, neuroinflammation, and cognitive impairment but enhances learning and memory in aluminum chloride-induced neurotoxicity in rats. Alzheimers Dement. 2025;21(5):e70223.
22. Shibabaw T. Omega-3 polyunsaturated fatty acids: anti-inflammatory and anti-hypertriglyceridemia mechanisms in cardiovascular disease. Mol Cell Biochem. 2021;476(2):993-1003.
23. Sarsilmaz M, Songur A, Ozyurt H, Kuş I, Ozen OA, Ozyurt B, et al. Potential role of dietary omega-3 essential fatty acids on some oxidant/antioxidant parameters in rat's corpus striatum. Prostaglandins Leukot Essent Fatty Acids. 2003;69:253-9.
24. von Schacky C, Harris WS. Cardiovascular benefits of omega-3 fatty acids. Cardiovasc Res. 2007;73:310-5.
25. Panda S, Kar A. Apigenin (4′,5,7-trihydroxyflavone) regulates hyperglycemia, thyroid dysfunction and lipid peroxidation in alloxan-induced diabetic mice. J Pharm Pharmacol. 2007;59(11):1543-8.
26. Ginwala R, McTish E, Raman C, et al. Apigenin, a natural flavonoid, attenuates EAE severity through the modulation of dendritic cell and other immune cell functions. J Neuroimmune Pharmacol. 2016;11(1):36-47.
27. Madunić J, Madunić IV, Gajski G, Popić J, Garaj-Vrhovac V. Apigenin: a dietary flavonoid with diverse anticancer properties. Cancer Lett. 2018;413:11-22.
28. Bi J, Chen C, Sun P, Tan H, Feng F, Shen J. Neuroprotective effect of omega-3 fatty acids on spinal cord injury induced rats. Brain Behav. 2019;9(8):e01339.
29. Kothari S, Singhal T. Docosahexaenoic acid administration ameliorates scopolamine-induced memory impairment in mice. Asian J Pharm Clin Res. 2018;11(6):349-52.
30. Mao XY, Yu J, Liu ZQ, Zhou HH. Apigenin attenuates diabetes-associated cognitive decline in rats via suppressing oxidative stress and nitric oxide synthase pathway. Int J Clin Exp Med. 2015;8(9):15506-13.
31. Nikbakht F, Khadem Y, Haghani S, Hoseininia H, Moein Sadat A, Heshemi P. Protective role of apigenin against Aβ 25-35 toxicity via inhibition of mitochondrial cytochrome c release. Basic Clin Neurosci. 2019;10(6):557-66.
32. Hooijmans CR, Pasker-de Jong PC, de Vries RB, Ritskes-Hoitinga M. The effects of long-term omega-3 fatty acid supplementation on cognition and Alzheimer's pathology in animal models of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2012;28(1):191-209.